A systematic review on the effectiveness of treatment with antidepressants in fibromyalgia syndrome

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CRD summary
This review concluded that amitriptyline was effective in reducing the symptoms of patients with fibromyalgia syndrome, and some other antidepressants may also be useful. Despite the methodological strengths of the review processes, the inappropriate statistical analyses mean that these findings cannot be considered reliable.

Authors' objectives
To review the efficacy of antidepressants as a treatment for fibromyalgia syndrome.

Searching
The following databases were searched to October 2007: MEDLINE, PsycINFO, SCOPUS, and the Cochrane Library. Search terms were reported. Reference lists from included papers and other relevant references were scanned.

Study selection
Controlled studies that compared antidepressant treatment with usual care, placebo or another well-defined treatment, in patients with a recognised diagnosis of fibromyalgia syndrome (or chronic widespread pain), were eligible for inclusion. Tricyclic and tetracyclic antidepressants, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors and monoamine oxidase inhibitors were considered; studies evaluating cyclobenzaprine or S-adenosylmethionine were excluded. All studies were required to report symptom specific outcome measures.

All of the included trials were based in outpatient clinics and most recruited from rheumatology departments. Median age of included participants was 46 years (range 30 to 53 years); the median duration of their symptoms was six years (range four to 16 years). Women made up the largest proportion of trials. Relatively few trials presented data on comorbidities. Nearly half of the trials were conducted in North America, with the remainder from South America and Europe. Most trials studied single antidepressants (tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors and monoamine oxidase inhibitors), only one trial explicitly prohibited the use of concomitant pain medication. Control groups included treatment with other antidepressants, placebo and non-pharmacological interventions. Median completion of treatment was between 81 and 85% across treatment and control groups. The main outcomes assessed were pain, fatigue, sleep, depression and quality of life.

Studies were screened independently by three reviewers for inclusion.

Assessment of study quality
Methodological quality was assessed using the 5-point Jadad scale plus additional items adapted from the CONSORT (Consolidated Standards of Reporting Trials) checklist: a priori definition of end points; power calculation; adequate statistical tests; adjustment for multiple tests; suitable for meta-analysis.

Validity assessment was performed by three independent reviewers; disagreements were resolved by consensus.

Data extraction
A standardised form was used for data extraction which appeared to include the presence or absence of a significant effect for each outcome measure reported, the percentage pain improvement in active treatment conditions, side effects, percentage of side effects, and drop-out rates due to side effects. Data were presented as percentages, medians and ranges as appropriate. Where a trial used more than one antidepressant, the results for each drug were considered separately.

Data were extracted by three independent reviewers; disagreements were resolved by consensus.
Methods of synthesis
Data were presented in tabular and narrative form. Results from the included trials were summed and compared using $\chi^2$ tests (proportions) or non-parametric tests for continuous data (Mann-Whitney U test, Kruskal-Wallis H test).

Results of the review
Twenty-six RCTs were included in this review (n=unclear). Twenty-two RCTs were parallel design and four used a cross-over design. Eight RCTs used a multi-centre recruitment design. Methodological quality was described as variable, with half of the studies scoring 4 or more points out of 5 on the Jadad scale. All RCTs were described as randomised, half reported a power calculation, but only nine used intention-to-treat analysis. Twelve RCTs used adequate statistical tests; one controlled for multiple testing. Seventeen RCTs provided data suitable for meta-analysis.

Overall results for all anti-depressants: Significant improvements were reported in 20 out of 24 RCTs for pain, 13 out of 18 RCTs for fatigue, 16 out of 19 RCTs for sleep, 11 out of 15 RCTs for depression, and 8 out of 11 trials for quality of life. Pain reduction ranged from 6 to 70% (median 29%). Improvement in quality of life ranged from 13 to 70% (median 30%).

RCTs with less than 4 points of the Jadad score reported more positive results than those with 4 points or more, p=0.003.

Authors’ conclusions
Amitriptyline reduced pain, fatigue and depression in patients with fibromyalgia syndrome and improved sleep and quality of life. Most selective serotonin reuptake inhibitors, and the serotonin-norepinephrine reuptake inhibitors duloxetine and milnacipran, were also probably effective.

CRD commentary
This review addressed a clear clinical question with relevant inclusion criteria. Appropriate databases were searched, apparently without language restriction, although there did not appear to have been an attempt to include grey literature, which may have introduced publication bias. Study selection, data extraction and quality assessment were all carried out by more than one reviewer, reducing the chance of error and/or bias being introduced.

The primary study results were not clearly reported (lack of actual results, simply indicated as 'significant'), which made it difficult to assess; the sample sizes were not easy to understand. RCTs appear to have been pooled inappropriately from a statistical perspective, without any weighting. Also, the results for each outcome were classified as significant or non-significant; valuable information was likely to have been lost by the collapsing of data into these categorical units.

There were further issues with the analysis but, overall, it appeared that the methods selected were not suitable and, as a result, the findings cannot be considered reliable and may not reflect the primary trials.

Implications of the review for practice and research
Practice: The authors stated that short-term treatment of patients with fibromyalgia syndrome using amitriptyline or another of the anti-depressants shown to be effective in RCTs can be recommended.

Research: The authors stated that trials of longer duration are required to investigate long-term efficacy, side effects and impact of medication on quality of life, among other outcomes. Cost-effectiveness studies are also recommended, as are studies on a more varied population.

Funding
German Research Network on Neuropathic Pain; University of Wurzburg.

Bibliographic details
Uceyler N, Hauser W, Sommer C. A systematic review on the effectiveness of treatment with antidepressants in fibromyalgia syndrome. Arthritis and Rheumatism (Arthritis Care and Research) 2008; 59(9): 1279-1298
Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.